(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: 0 463 833 A2

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 91305669.3

(22) Date of filing: 24.06.91

(51) Int. Cl.[5]: A61K 9/26, A61K 9/22, A61K 9/20, A61K 9/02, A61K 31/485, A61K 47/12

(30) Priority: 27.06.90 HU 400790

(43) Date of publication of application: 02.01.92 Bulletin 92/01

(84) Designated Contracting States: AT BE CH DK FR GB IT LI NL

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(54) Controlled release pharmaceutical preparation and process for preparing same.

(57) Controlled release pharmaceutical preparations are prepared by homogenizing an organic or inorganic pharmaceutical active substance such as an opium alkaloid or its salts, an opium antagonist or its salts, an aliphatic or aromatic amine derivative or its salts, a phenolate type medicament, or Zn, Fe, Mg, K, Na salts, a fatty acid or its salt necessary to achieve a continuous phase transfer and an ethylene vinyl acetate copolymer and formulating the resulting homogeneous mixture by

a) direct compressing or
b) admixing with a solvent or
c) using a second, auxiliary polymer.

The preparations are suitable for oral or rectal administration or for tissue implantation.

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The present invention relates to a controlled release pharmaceutical preparation and a process for preparing same.

According to the present invention matrix systems comprising ethylene-vinyl acetate copolymer are provided which are useful for preparing a controlled release preparation containing the active ingredient in ionic form.

Technical background

The medical use of ethylene-vinyl acetate copolymers is well known in the art [Biomaterials 2 201 (1981) J.Biomedical Materials Research 15 267 (1981)]. Controlled release pharmaceutical preparations for treating glaucoma, diabetes as well as controlled release contraceptives were prepared by using this copolymer. Because of its high biocompatibility [J. Biomedical Materials Research 15 267 (1981)] various human applications of this copolymer have been permitted by the FDA.

In view of the above described it is surprising that only a few oral applications are reported in the art and even these are developed for use as a mycoderma adhesive flexible films put into the mouth cavity [Japanese Kokai Tokkyo Koka JP 6305, 756 8805,756, ibid, 61 93, 113 8693,113, ibid 6354, 318 885 4318] or in dentistry [European Patent Application EP 268464.]

No typical oral application, e.g. use as a base for tablets has been described.

In order to provide a preparation for oral administration we have selected the morphine sulphate as an example for the active ingredient because retarding the release of this active substance is essential in analgetic treatment and, on the other hand, this medicament represents a whole family of salt-like active substances with excellent water solubility.

Various polymer systems are proposed for retarding the release of morphine sulphate. For example in J. Pharmacol. Methods 1(2) 21 (1978) and J. Pharm. Sci. 69(8) 980 (1980) dimethylsiloxane, in European Patent Application EP 205 282 a mycoderma adhesive cellulose composition, in French Patent Application Fr. 2,576 213 sulphate and carboxylate anion exchanger, in Rev. Asoc. Esp. Farm. Hosp. 11(1) 111 (1987) PVC and Methacel K-15 M, in ACS. Symp. Ser. 348 (1987) polyethylene oxide and in Br.J. Anaesth 61 221 (1988) crosslinked ethylene oxide are described. According to the above prior art references these polymer systems are suitable for retarding the release of the morphine sulphate but do not ensure simultaneously th wide variability of the dissolution profile and th dissoluti n rate.

Disclosure of th inv ntion

The pres nt invention is based n the recognition that ethylene vinyl-acetate copolymers can be mixed with both polar and apolar substances without phase s parati n, by using suitable additives and technics, due to their ability to double swelling.

As a result, both rate and shape of dissolution can be controlled.

Detailed description of the invention

According to the present invention a process is provided for retarding the release of an active substance comprising the steps of homogenizing organic or inorganic pharmaceutical active substances, such as an opium alkaloid or its salts, an opium antagonist or its salts, an aliphatic or aromatic amine derivative or its salts, a phenolate type medicament, or Zn, Fe, Mg, K, Na salts, a fatty acid or its salts necessary to the continuous phase transfer, and ethylene vinyl acetate copolymer and formulating the resulting homogeneous mixture by

a) direct compressing or

b) admixing with a solvent or

c) using a second, auxiliary polymer,

and by adding conventional pharmaceutical additives into a controlled release dosage form suitable for oral or rectal administration or for tissue implantation.

a) A homogeneous powdered mixture of suitable composition may be pressed simply to a swelling matrix. The dissolution rate and shape can be changed depending on the composition of th powdered mixture.

In order to demonstrate the possibilities of controlling the dissolution rate and shape according to the invention, comparative tests have been carried out with MST 30 mg (Mundidol) retard film tablets. The matrix of Example 1 of the present invention has shown the same dissolution rate and shape (considering the margin of experimental error) as the MST 30 mg (Mundidol) preparation.

b) A uniform powdered mixture of suitable composition mixed with an alcohol gives a gel or pastelike substance which may be formulated by physical methods well known in the art into the desired solid dosage forms.

In accordance with the invention it has been found that both rate and shape of the dissolution can be controlled not only by changing the composition of the powdered mixture, but also by changing the amount of the solvent applied.

c) Since an ethylene vinyl acetate copolymer can be affixed with apolar rubbery substances, such rubbery auxiliary polymers were used in order to achiev forms being stable in biological systems and to avoid the breakdown of said forms.

It has been found that the dissolution rate of e.g. the morphin sulphate depends on th amount of th rubber solution, th rati of th solvent used for dilu-

tion as well as on the time of th triturating. By using a larger amount of the rubber solution, even a retardation of several days is possible. The resulting film makes other types of administration (such as tissue implantation, rectal administering) possible. Natural rubber may be replaced also by different synthetic rubbers. In case of equal amounts and concentration of rubber solutions the natural rubber shows the most slowly dissolution indicating the importance of the molecular weight distribution in controlling the dissolution. A large molecular weight distribution is advantageous.

By using a large amount of solvent, a film is obtained in the course of mixing and subsequent drying which cannot be powdered at room temperature but may be compressed into tablets after appropriate crushing.

The main advantages of the process according to the present invention may be summarized as follows:

1) Due to the amphiphilic properties of the carrier, it is possible to control the release of both organic and inorganic salt-like active substances.
2. The dissolution shape and rate can be varied in a wide range according to the therapeutic needs and can be adjusted exactly.
3. The whole quantity of the active ingredient is set free.
4. The carrier is highly biocompatible.
5. The process can be realized at room temperature, thus it is suitable for retarding substances being sensitive to heat.
6. The process is simple, no special installation is needed, the traditional steps of preparing a pharmaceutical composition may be used.
7. The carrier remaining after dissolution is powdery in cases a) and b) and becomes rubbery after shrinking in case c).

The following non-limiting examples illustrate further the invention.

Example 1

Morphine sulphate pentahydrate (3.75 g), magnesium stearate (0.55 g) and ethylene vinyl acetate copolymer (Vinnapas Re 530Z, 15.62 g) were homogenized in an agate mortar. The resulting powdered blend may directly be cold compressed into tablets.

Example 2

Morphine sulphate (6.0 g), magnesium stearate (1.6 g), cellulose (1.6 g) and ethylene vinyl acetate copolymer (Vinnapas RE 530Z, 10.8 g) were placed into an agate mortar , homog nized and triturated with isopropyl alcohol (6.0 mL). The resulting w t powdered mixture was dried in vacuo at room temperature, while triturating several times. The dried blend may be powdered and compressed into tablets in a desired manner. The dissolution rate can be controlled by the amount of the isopropyl alcohol. Wh n the ratio of powdered blend to isopropyl alcohol was 1:1, the powdered blend could be neaded to a paste. After drying and applying in an appropriate manner a film was obtained.

Example 3

a) Natural rubber (SMR 20 NR, 1 g) was dissolved in toluene (100 mL) under reflux during 24 hours. The resulting slightly yellow solution was cooled and the small quantity of floating solid material was allowed to sedimentate. Sedimentation can be accelerated by centrifugation. 12 mL of the clear part of the solution was diluted by 10 mL of toluene and the whole quantity was used in the following step.

b) Morphine sulphate (3.05 g), magnesium stearate (0.58 g), cellulose powder (0.44 g) and ethylene vinyl acetate copolymer (Vinnapas RE 530Z, 5.81 g) were placed into an agate mortar and homogenized. The powdered mixture was triturated with the solution prepared according to step a). A wet suspension was obtained which was dried in vacuo while triturating several times. The resulting matrix could be tabletted directly.

The dissolution of the active ingredients was tested according to pH. Hg. VII (K/g 15.2.5), in 0.1 N HCl, by 100^{+} l/min rpm. The results are shown in Figure 1.

Claims

1. A process for retarding the release of a pharmaceutical active substance by using ethylene vinyl-acetate copolymer comprising the steps of homogenizing an organic or inorganic pharmaceutical active substance, a fatty acid or its salt necessary to achieve a continuous phase transfer and an ethylene vinyl acetate copolymer and formulating the resulting homogeneous mixture by
   a) direct compressing or
   b) admixing with a solvent or
   c) using a second, auxiliary polymer, and by adding conventional pharmaceutical additives into a controlled release dosage form.

2. The process according to claim 1 wherein said organic active substance is selected from the group comprising an opium alkaloid and its salts, an opium antagonist and its salts, an aliphatic or aromatic amine derivative and its salts and a phenolate typ medicament.

3. The process according to claim 1 wh rein said

inorganic active substance is selected from th group comprising a Zn, Fe, Mg, K and Na salt.

4. The process according to claim I wherein said fatty acid or its salt necessary to the continuous phase transfer is a fatty acid containing 10 to 40 carbon atoms or its alkali, alkali-earth or earth metal salts.

5. The process according to claim 1 variant a) comprising the steps of homogenizing the active substance, the ethylene vinyl acetate copolymer, the suitable fatty acid salt and the conventional pharmaceutical additives and subjecting the resulting mixture to a cold, direct pressing.

6. The process according to claim 1, variant b) comprising the steps of homogenizing the active substance, the ethylene vinyl acetate copolymer, the suitable fatty acid salt and the conventional pharmaceutical additives, and mixing the resulting blend with a solvent selected from an alcohol containing 1 to 15 carbon atoms thus obtaining a gel- or paste-like substance.

7. The process according to claim 6 wherein said gel-like substance is formulated into a dosage form suitable for oral or rectal administration or for tissue implantation.

8. The process according to claim 1, variant c) comprising the steps of homogenizing the active substance, the ethylene vinyl acetate copolymer, the suitable fatty acid salt and the conventional pharmaceutical additives, and mixing the resulting blend with a solution of an auxiliary polymer selected from the group of natural rubbers or a synthetic rubber in an apolar solvent, thus obtaining a gel- or paste-like substance.

9. The process according to claim 8 wherein said gel-like substance is formulated into a dosage form suitable for rectal administration or for tissue implantation.

10. A preparation prepared according to claim 5 or 7 suitable for oral or rectal administration or for tissue implantation.

11. A preparation prepared according to claim 9 suitable for rectal administration or for tissue implantation.

Dissolution of the active substance from preparations prepared according to process variant a, b, and c of the invention.

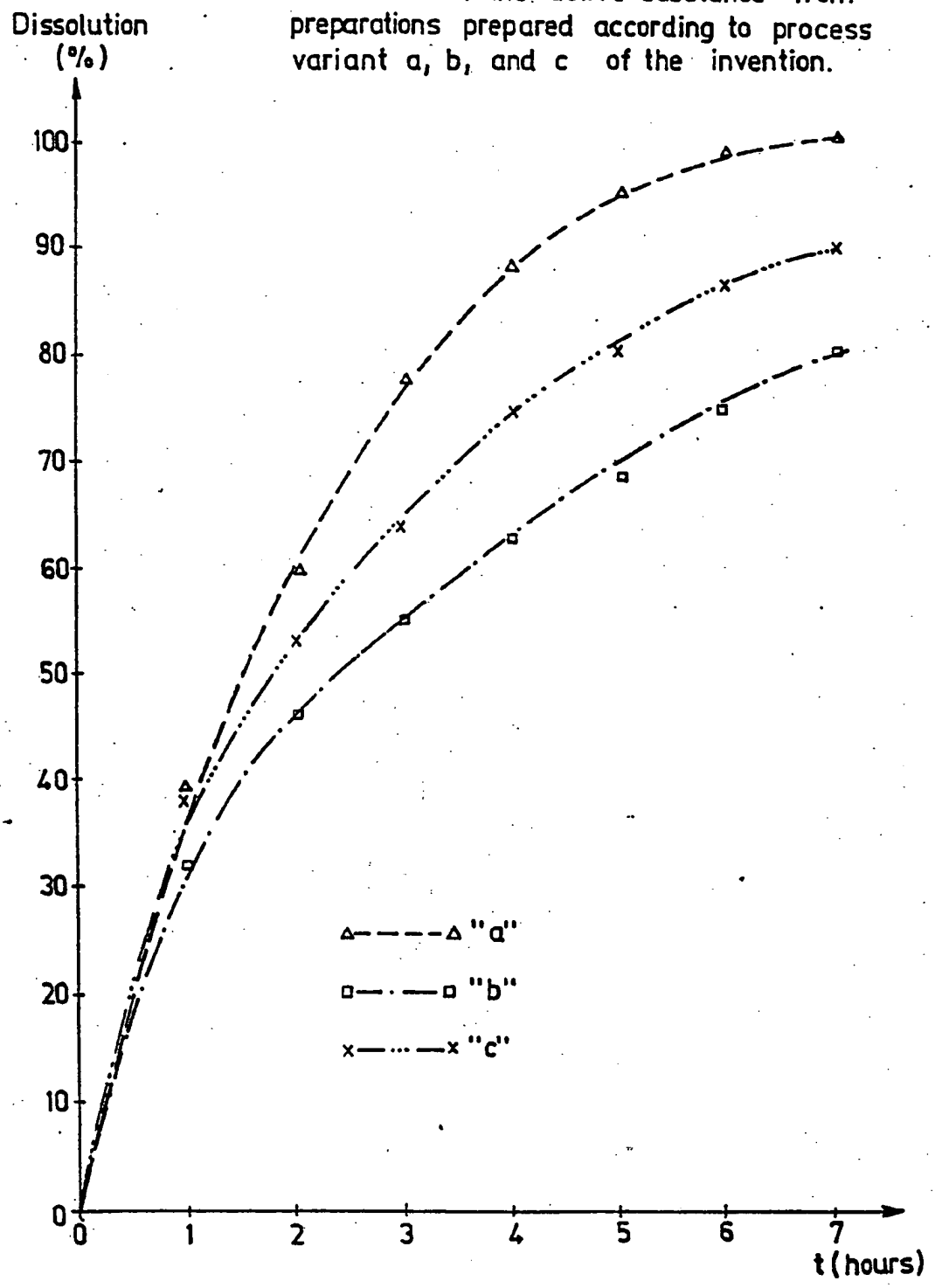

Fig.1

Dissolution of the active substance from preparations prepared according to process variant a, b, and c of the invention.

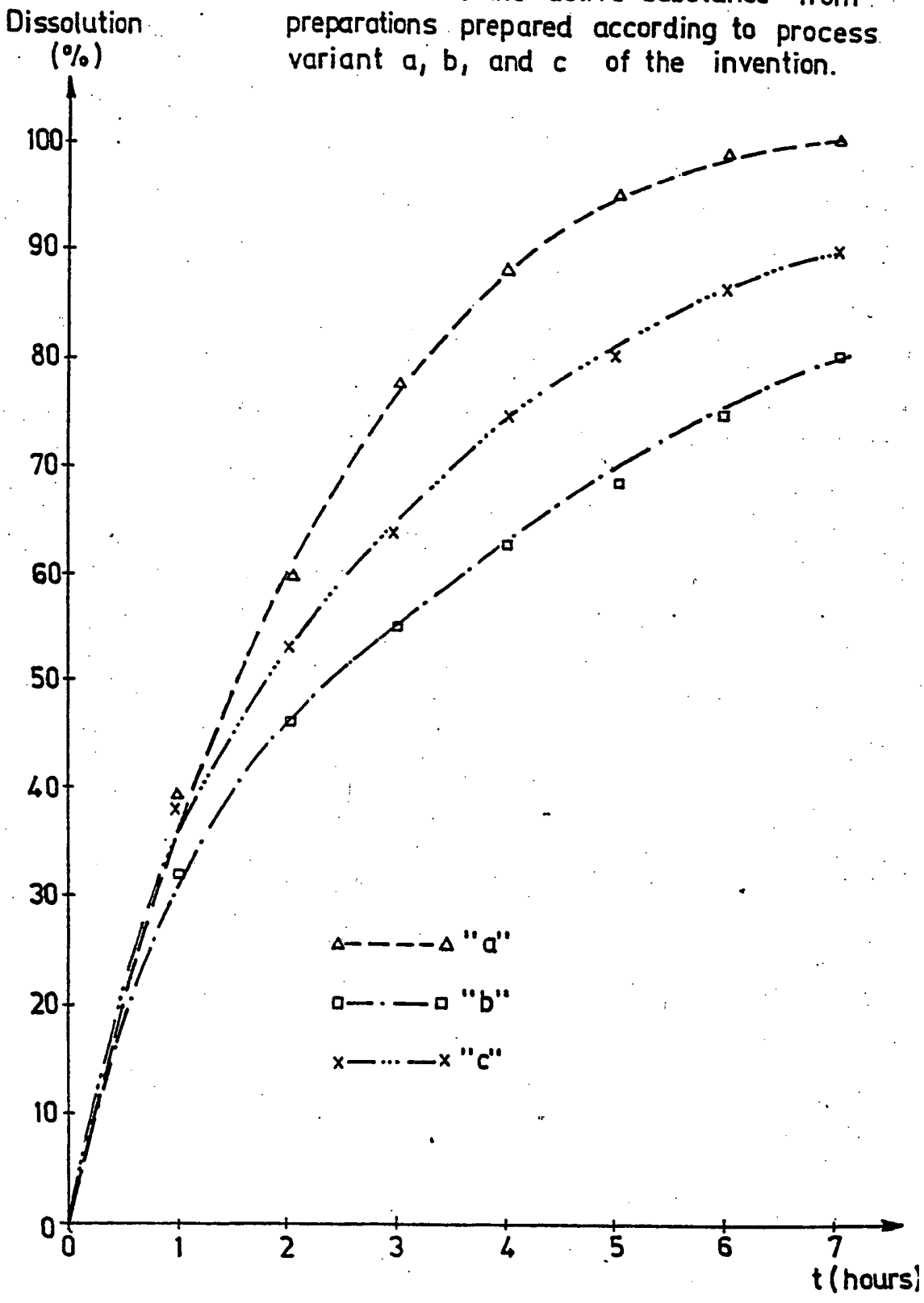

Fig.1